POSTER NUMBER

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Rifaximin Monotherapy Has Significantly Reduced the Risk of Overt Hepatic Encephalopathy Recurrence Versus Lactulose Monotherapy in Patients With Cirrhosis and a History of Previous Episode(s): A Post Hoc Analysis of Randomized Trials

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INTRODUCTION

- Rifaximin (Tixteller®/Xifaxan®) is indicated in multiple countries for the reduction in risk of overt hepatic encephalopathy (OHE) recurrence in adults
- Lactulose monotherapy (titrated to achieve 2-3 bowel movements daily) is recommended as secondary prophylaxis after an initial episode of OHE[1,2]
  - Rifaximin is recommended as add-on therapy when additional episodes occur[1,2]
- Nonadherence to lactulose therapy can precipitate hepatic encephalopathy (HE) recurrence[3,4]
  - In a 2023 study (N=129), HE-related hospital admission rates were numerically greater in patients nonadherent (Morisky Adherence Scale 8 score ≥2) to lactulose versus those who were adherent (41.7% vs 24.4%; *P*=0.07)[5]
  - Potential barriers to lactulose adherence include gastrointestinal (GI) adverse effects (eg, diarrhea, nausea, and vomiting), dosing and volume requirements, and unpleasant taste[5,6]
  - GI-related adverse effects, such as diarrhea, can lead to dehydration or electrolyte imbalances, which are also precipitating factors of OHE[6,7]
- These lactulose-related issues indicate that alternative management strategies to reduce the risk of OHE recurrence may be required

AIM

- To compare the efficacy and safety of rifaximin monotherapy versus lactulose monotherapy for reducing the risk of OHE recurrence in patients with cirrhosis and a history of OHE

METHODS

- Data were pooled post hoc from 2 randomized trials (one phase 3 double-blind trial[8] and one phase 4 open-label trial) of adults who had cirrhosis and a history of OHE occurrence during the previous 6 months and were currently in OHE remission (Conn score ≤1)

Treatment and Assessments

- Data were analyzed for patients who received rifaximin 550 mg twice daily (BID) (ie, no concomitant lactulose [phase 3 or 4 trials]) or lactulose (titrated to 2-3 soft stools/d) plus placebo (ie, lactulose monotherapy [phase 3 trial]) for up to 6 months*
- In the phase 3 trial, assessments occurred on Day 0 (±1); Days (±2) 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168; and during the follow-up visit (14±2 days after the end of treatment)
- In the phase 4 trial, assessments occurred on Day 1; Days (±2) 28, 56, 84, 112, 140, and 168; and during the follow-up visit (14±2 days after the end of treatment)
- The primary efficacy endpoint was time to first breakthrough OHE episode (Conn score ≥2) and a secondary endpoint was time to first HE-related hospitalization (original endpoints in both trials)
- Hazard ratio (HR) estimates were obtained using a Cox proportional hazards model with effect for treatment, and *P* values were based on the score statistic

*In the phase 3 trial, rifaximin 550 mg BID or placebo was administered with optional lactulose; in the phase 4 trial, rifaximin 550 mg BID or rifaximin 550 mg BID plus lactulose was administered. Only patients receiving rifaximin alone or lactulose + placebo ("lactulose alone") were included in the current analysis.

RESULTS

- A total of 270 patients were treated with rifaximin monotherapy (n=125) or lactulose monotherapy (n=145; **Table 1**)

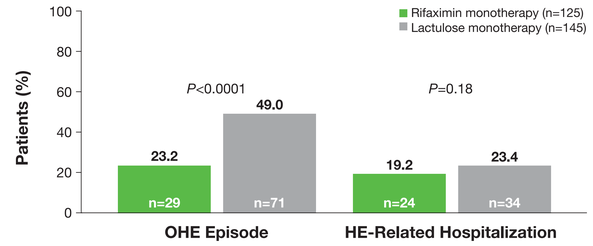
Table 1. Demographic and Baseline Disease Characteristics

Characteristic	Rifaximin Monotherapy (n=125)	Lactulose Monotherapy (n=145)
Age, y, mean (SD)	58.2 (9.5)	56.6 (9.3)
Male, n (%)	75 (60.0)	99 (68.3)
Race, n (%)		
White	113 (90.4)	126 (86.9)
Black	8 (6.4)	5 (3.4)
Asian	2 (1.6)	7 (4.8)
Other	2 (1.6)	7 (4.8)
Baseline MELD score		
Mean (SD)	12 (4)	13 (4)
Median (range)	12 (6-24)	12 (6-23)
Child-Pugh class, n (%)		
A	54 (43.2)	49 (33.8)
B	64 (51.2)	67 (46.2)
C	7 (5.6)	13 (9.0)
Missing data	0	16 (11.0)
Baseline Conn score, n (%)		
0	86 (68.8)	98 (67.6)
1	39 (31.2)	47 (32.4)
Duration of current OHE remission, d, mean (SD)	89.7 (56.0)	73.6 (52.0)

MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

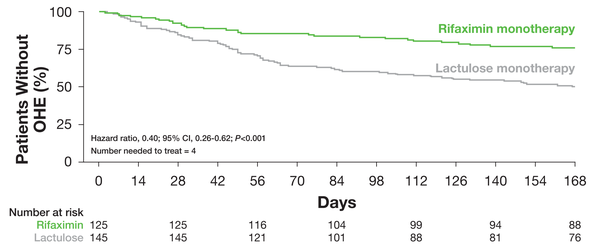
- Significantly fewer patients treated with rifaximin monotherapy experienced an OHE episode compared with lactulose monotherapy (23.2% vs 49.0%, respectively; *P*<0.0001 [**Figure 1**])
- Rifaximin monotherapy reduced the risk of a breakthrough OHE event by 60% versus lactulose monotherapy during 6 months of treatment, with a number needed to treat of 4 (HR, 0.40 [**Figure 2**])

Figure 1. Percentage of Patients Experiencing an OHE Episode or an HE-Related Hospitalization



HE = hepatic encephalopathy; OHE = overt hepatic encephalopathy.

Figure 2. Time to First Breakthrough OHE Episode



OHE = overt hepatic encephalopathy.

- Fewer patients treated with rifaximin monotherapy had an HE-related hospitalization compared with lactulose monotherapy, although the difference was not statistically significant (19.2% vs 23.4%, respectively, *P*=0.18 [**Figure 1**])
- The most commonly reported adverse events overall (excluding HE) were nausea, fatigue, and peripheral edema (**Table 2**)
  - A higher percentage of patients treated with lactulose monotherapy compared with rifaximin monotherapy reported diarrhea (14.5% vs 4.8%) and vomiting (9.7% vs 4.8%)
- Discontinuation from study participation was higher in the lactulose monotherapy group (62.1%) versus the rifaximin monotherapy group (36.0%), most commonly due to OHE occurrence

Table 2. Summary of Adverse Events

Patients With an AE, n (%)	Rifaximin Monotherapy (n=125)	Lactulose Monotherapy (n=145)
≥1 AE	105 (84.0)	126 (86.9)
≥1 drug-related AE	8 (6.4)	35 (24.1)
≥1 serious AE	44 (35.2)	60 (41.4)
Deaths	2 (1.6)	10 (6.9)
Most common AEs*		
Nausea	17 (13.6)	21 (14.5)
Fatigue	16 (12.8)	18 (12.4)
Peripheral edema	20 (16.0)	13 (9.0)
Constipation	18 (14.4)	10 (6.9)
Diarrhea	6 (4.8)	21 (14.5)
Headache	9 (7.2)	17 (11.7)
Insomnia	14 (11.2)	11 (7.6)
Ascites	9 (7.2)	15 (10.3)
Muscle spasms	10 (8.0)	10 (6.9)
Vomiting	6 (4.8)	14 (9.7)
Abdominal pain	8 (6.4)	11 (7.6)
Asthenia	6 (4.8)	12 (8.3)
Anemia	12 (9.6)	6 (4.1)
Urinary tract infection	14 (11.2)	14 (9.7)

*Ranked by the highest incidence in the overall population (≥6.7%), then alphabetically (excluding hepatic encephalopathy).
AE = adverse event.

CONCLUSIONS

- Rifaximin monotherapy was well tolerated and associated with significantly fewer episodes of OHE recurrence than lactulose monotherapy in patients with cirrhosis and a history of OHE
- Data suggest rifaximin monotherapy could be a viable management option for OHE recurrence risk reduction in appropriate patients

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